For #09/919,196

```
? ds
Set     Items   Description
S1        187   PARENT?(5N)(LNCAP OR PC(W)3 OR DU(W)145)
S2        128   PARENT? (5N)LNCAP
S3     102938   NEUROENDOCRINE OR NE
S4          3   S1 AND S3
S5          2   RD (unique items)
S6       7287   LNCAP
S7        183   S3 AND S6
S8        147   S7 AND PY<=2001
? s s8 and py<2001
Processing
            147  S8
       37913231  PY<2001
     S9     114  S8 AND PY<2001
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...examined 50 records  (100)
...completed examining records
    S10      59  RD (unique items)
```

10/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10372578 99374667 PMID: 10447001

Acquisition of **neuroendocrine** characteristics by prostate tumor cells is reversible: implications for prostate cancer progression.

Cox M E; Deeble P D; Lakhani S; Parsons S J

Cancer Center and Department of Microbiology, University of Virginia Health Sciences Center, Charlottesville 22908, USA.

Cancer research (UNITED STATES) Aug 1 **1999**, 59 (15) p3821-30,
ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: PO1 40042; PHS; R21 69848; PHS; RO1 76649; PHS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Neuroendocrine (**NE**) cells occur as scattered foci within prostatic adenocarcinoma, similar to their distribution within ductal epithelial cells of the normal prostate. However, the density of **NE** cells is often greater in prostate carcinomas than in normal tissue, and the frequency of **NE** cells correlates with tumor grade, loss of androgen sensitivity, autocrine/paracrine activity, and poor prognosis. Although **NE** cells are nonmitotic, proliferating cells are found in direct proximity to them, suggesting that **NE** cells provide paracrine stimuli for surrounding carcinoma cells. In vitro, differentiation of the **LNCaP** and PC3M prostatic tumor cell lines to a **NE** phenotype can be induced by dibutyryl cyclic AMP (cAMP), suggesting that physiological agents that increase intracellular concentrations of cAMP might regulate **NE** differentiation in vivo. Indeed, we demonstrate in this report that **LNCaP** cells acquire **NE** characteristics in response to treatment with physiological and pharmacological agents that elevate intracellular cAMP, agents such as epinephrine, isoproterenol, forskolin, and dibutyryl cAMP. The androgen-independent **LNCaP**-derived cell line C4-2 also responded to these agents, indicating that cells representing later stages of tumor progression are also capable of differentiation. The **NE** phenotype in this study was monitored by the appearance of dense core granules in the cytoplasm, the extension of neuron-like processes, loss of mitogenic activity, and expression of the **NE** markers neuron-specific enolase, parathyroid hormone-related peptide, neurotensin, serotonin, and chromogranin A. However, contrary to previous reports, we observed rapid loss of the **NE** phenotype in both **LNCaP** and C4-2 cells upon withdrawal of inducing agents. Withdrawal also resulted in a rapid, dramatic increase in tyrosine kinase and mitogen-activated protein kinase activities, suggesting that activation of these intracellular signaling enzymes may be important for reentry into the cell cycle. Together, these results indicate that chronic cAMP-mediated signaling is required to block proliferation of prostate tumor cells and to induce **NE** differentiation.

Acquisition of **neuroendocrine** characteristics by prostate tumor cells is reversible: implications for prostate cancer progression.

Aug 1 **1999**,

Neuroendocrine (**NE**) cells occur as scattered foci within prostatic adenocarcinoma, similar to their distribution within ductal epithelial cells of the normal prostate. However, the density of **NE** cells is often greater in prostate carcinomas than in normal tissue, and the frequency of **NE** cells correlates with tumor grade, loss of androgen sensitivity, autocrine/paracrine activity, and poor prognosis. Although **NE** cells are nonmitotic, proliferating cells are found in direct proximity to them, suggesting that **NE** cells provide paracrine stimuli for surrounding carcinoma cells. In vitro, differentiation of the **LNCaP** and PC3M prostatic tumor cell lines to a **NE** phenotype can be induced by dibutyryl cyclic AMP (cAMP), suggesting that physiological agents that increase intracellular concentrations of cAMP might regulate

NE differentiation in vivo. Indeed, we demonstrate in this report that **LNCaP** cells acquire **NE** characteristics in response to treatment with physiological and pharmacological agents that elevate intracellular cAMP, agents such as epinephrine, isoproterenol, forskolin, and dibutyryl cAMP. The androgen-independent **LNCaP**-derived cell line C4-2 also responded to these agents, indicating that cells representing later stages of tumor progression are also capable of differentiation. The **NE** phenotype in this study was monitored by the appearance of dense core granules in the cytoplasm, the extension of neuron-like processes, loss of mitogenic activity, and expression of the **NE** markers neuron-specific enolase, parathyroid hormone-related peptide, neurotensin, serotonin, and chromogranin A. However, contrary to previous reports, we observed rapid loss of the **NE** phenotype

Multipathways for transdifferentiation of human prostate cancer cells into **neuroendocrine**-like phenotype.

Zelivianski S; Verni M; Moore C; Kondrikov D; Taylor R; Lin M F
Department of Biochemistry/Molecular Biology, University of Nebraska Medical Center, Omaha 68198, USA.

Biochimica et biophysica acta (Netherlands) May 28 **2001**, 1539 (1-2) p28-43, ISSN 0006-3002 Journal Code: 0217513
Contract/Grant No.: CA72274; CA; NCI; CA88184; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The **neuroendocrine** (**NE**) cell is a minor cell population in normal human prostate glands. The number of **NE** cells is increased in advanced hormone-refractory prostate carcinomas (PCA). The mechanism of increased **NE** cell population in these advanced tumors is poorly understood. We examined molecular mechanisms which may be involved in the regulation of the transdifferentiation process of human PCA cells leading to a **NE** phenotype. We compared PCA cell lines **LNCaP** and PC-3 in the following medium conditions: steroid-reduced (SR), interleukin-6 (IL-6)-supplemented, or dibutyrate cAMP (db-cAMP)-supplemented. We found that androgen-responsive C-33 **LNCaP** cells responded to all treatments, having a neuronal-like morphology. In contrast, C-81 **LNCaP** cells, having a decreased androgen responsiveness, had a less pronounced effect although followed a similar trend. Androgen-unresponsive PC-3 cells showed little change in their morphology. Grown in the SR condition, the level of neuron-specific enolase (NSE), a marker of neuronal cells, was upregulated in C-33 **LNCaP** cells, while to a lesser degree in the presence of IL-6. In the presence of db-cAMP, the NSE level in C-33 cells was decreased, lower than that in control cells. An opposite effect was observed for C-81 **LNCaP** cells. Nevertheless, the NSE level was only elevated in db-cAMP-treated PC-3 cells, but no change was found in PC-3 cells grown in the SR- or IL-6-supplemented medium. Thus, a similar gross phenotypic change may correlate with differential molecular expressions. We also analyzed the expression of protein tyrosine phosphatase alpha (RPTPalpha) since it plays a critical role in normal

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? s parent?(5n)(LNCAP or PC(w)3 or DU(w)145)
Processing
          392796  PARENT?
            7287  LNCAP
          562134  PC
         8717350  3
            5180  PC(W)3
          386088  DU
           41136  145
            2532  DU(W)145
      S1     187  PARENT?(5N)(LNCAP OR PC(W)3 OR DU(W)145)
? s parent? (5n)lncap
          392796  PARENT?
            7287  LNCAP
      S2     128  PARENT? (5N)LNCAP
? s neuroendocrine or ne
           47384  NEUROENDOCRINE
           56707  NE
      S3  102938  NEUROENDOCRINE OR NE
? s s1 and s3
             187  S1
          102938  S3
      S4       3  S1 AND S3
? rd
>>>Duplicate detection is not supported for File 340.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S5       2  RD (unique items)
? t s5/3,k,ab/1-2
```

7753862 93278688 PMID: 7684949

Autocrine regulation of prostate-specific antigen gene expression in a human prostatic cancer (LNCaP) subline.

Hsieh J T; Wu H C; Gleave M E; von Eschenbach A C; Chung L W

Department of Urology, University of Texas M. D. Anderson Cancer Center, Houston 77030.

Cancer research (UNITED STATES) Jun 15 1993, 53 (12) p2852-7, ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: CA 56307; CA; NCI; CA 59939; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Prostate-specific antigen (PSA), a M(r) 34,000 serine protease, is recognized as a useful marker for the detection and prognosis of patients with prostate cancer. Although serum PSA is an excellent prognostic indicator, an increasing number of factors were found to regulate the PSA expression of prostatic cancer cells, which include androgenic steroids, the growth factors (GFs) and the extracellular matrix. The purpose of this study is to define a novel protein factor that may be responsible for regulating PSA expression by androgen-independent (AI) human prostate cancer cells. We have established a **LNCaP** subline (C4) from a **parental LNCaP** tumor grown in a castrated host. The C4 subline overexpressed PSA mRNA and protein. Serum-free conditioned medium (CM) isolated from the C4 subline is able to stimulate PSA gene expression in **parental LNCaP** cells in a concentration-dependent manner. This autocrine PSA-inducing activity was found to be organ specific because CMs from other fibroblast cell lines (such as bone, prostate, kidney, and lung fibroblasts) and the CMs from several prostatic carcinoma cell lines (such as **parental LNCaP** , PC-3, DU-145) and a bladder transitional carcinoma cell line (WH) fail to exhibit similar activity. The activity of the CM from the C4 subline cannot be substituted by GFs such as TGF-alpha, TGF-beta, bFGF, HGF, KGF, or NGF; neuropeptide (bombesin/GRP); secondary messenger analogue (dibutyryl cAMP); beta 2-adrenergic agonist (isoproterenol); or alpha 1-adrenergic agonist (phenylephrine), indicating that the factor(s) may be a novel prostate-specific autocrine factor

10/3,K,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10458659 99452569 PMID: 10524938

Transdifferentiation of prostate cancer cells to a **neuroendocrine** cell phenotype in vitro and in vivo.

Burchardt T; Burchardt M; Chen M W; Cao Y; de la Taille A; Shabsigh A; Hayek O; Dorai T; Buttyan R

Department of Urology, College of Physicians and Surgeons of Columbia University, New York, New York, USA.

Journal of urology (UNITED STATES) Nov **1999**, 162 (5) p1800-5, ISSN 0022-5347 Journal Code: 0376374

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

PURPOSE: To better understand the source of **neuroendocrine** cells associated with human prostate cancer progression, we studied the ability of a cultured prostate cancer cell line, **LNCaP**, to transdifferentiate into **neuroendocrine** -like cells in vitro and in vivo. MATERIALS AND METHODS: Cyclic AMP concentrations were measured in extracts of **LNCaP** cells cultured in the presence of normal or hormone-deficient medium (containing charcoal-stripped serum) with the use of an immunoassay. Quantitative RT-PCR procedures were used to determine whether hormone depletion affects TGF-beta2 mRNA expression. Western blotting procedures (for neuron specific enolase [NSE]) were used to determine whether TGF-beta2 supplementation or antibody neutralization might affect the ability of cultured **LNCaP** cells to transdifferentiate to **neuroendocrine**-like cells. Finally, tumors formed from **LNCaP** cells xenografted into male nude mice were evaluated for the presence of **neuroendocrine** cells (prior and subsequent to castration of the host mouse) using an immunohistochemical stain for chromogranin A. RESULTS: **LNCaP** cells cultured in a hormone-deficient medium have a mean 9-fold increase in cyclic AMP ($p = 0.02$) and a significant decline in the expression of TGF-beta2 mRNA when compared with cells grown in normal medium. Supplementation or depletion of TGF-beta2 did not affect the **neuroendocrine** conversion of **LNCaP** cells as assessed by NSE expression patterns. **LNCaP** tumors growing in castrated male nude mice were found to have significantly increased numbers of chromogranin A positive **neuroendocrine** cells (46/high powered field) when compared with tumors growing in intact male mice (3/high powered field) ($p = 0.0038$). CONCLUSIONS: Exposure of **LNCaP** cells to a hormone deficient medium drastically increased cyclic AMP production and this may identify the biochemical pathway through which hormone depletion induces a **neuroendocrine** conversion of prostate cancer cells. Hormone depletion also reduced TGF-beta2 mRNA expression and this finding was consistent with our inability to demonstrate any effect of TGF-beta2 on **neuroendocrine** conversion in vitro. Finally, our demonstration of increased **neuroendocrine** cells found in **LNCaP** tumors growing in castrated immunodeficient mice suggests that the **neuroendocrine** cells associated with advanced human prostate tumors in vivo, arise from prostate cancer cells through the transdifferentiation process.

Transdifferentiation of prostate cancer cells to a **neuroendocrine** cell phenotype in vitro and in vivo.

Nov **1999**,

PURPOSE: To better understand the source of **neuroendocrine** cells

IALOG(R)File 155:MEDLINE(R)

08110083 94261579 PMID: 8202489

Terminal **neuroendocrine** differentiation of human prostate carcinoma cells in response to increased intracellular cyclic AMP.

Bang Y J; Pirnia F; Fang W G; Kang W K; Sartor O; Whitesell L; Ha M J; Tsokos M; Sheahan M D; Nguyen P; et al

Clinical Pharmacology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Jun 7 **1994**, 91 (12) p5330-4, ISSN 0027-8424 Journal Code: 7505876

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Recent clinicopathologic studies have shown that many prostatic adenocarcinomas express focal **neuroendocrine** differentiation and that **neuroendocrine** differentiation is most apparent in advanced anaplastic tumors. While studying growth-regulatory signal transduction events in human prostate carcinoma cell lines, we found that in two of four cell lines, the androgen-sensitive line **LNCaP** and the highly metastatic androgen-independent line PC-3-M, elevation of cAMP through addition of cAMP analogues or phosphodiesterase inhibitors induced a markedly neuronal morphology. Also in **LNCaP** cells ultrastructural analysis showed that cAMP induced the appearance of neurosecretory cell-like dense-core granules. Phenotypic analysis of untreated **LNCaP** and PC-3-M cells showed that both cell lines express markers of the neural crest including S-100, chromogranin A, pp60c-src, and neuron-specific enolase as well as the epithelial marker KS1/4 and stage-specific embryonic antigen 4. In PC-3-M cells, cAMP markedly elevated neuron-specific enolase protein and caused an increase in the specific activity of the **neuroendocrine** marker pp60c-src, and in both cell lines expression of KS1/4 and stage-specific embryonic antigen 4 was down-regulated. In addition to effects on lineage markers, cAMP treatment induced G1 synchronization, growth arrest, and loss of clonogenicity, indicating terminal differentiation. Our data provide direct evidence of plasticity i

976309 BIOSIS NO.: 199799597454
Differential expression and regulation of p53 in human prostatic cells.
AUTHOR: Hsieh Tze-Chen; Wu Joseph M(a)
AUTHOR ADDRESS: (a)Dep. Biochem. Molecular Biol., New York Med. Coll., Basic Sci. Build., Valhalla, NY 10595**USA
JOURNAL: International Journal of Oncology 10 (6):p1109-1112 **1997**
ISSN: 1019-6439
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Although genetic analysis has convincingly shown the association possibly existing between alterations in p53 tumor suppressor gene and a broad spectrum of human tumors including prostate cancer, surprisingly little is known about ways in which p53 at the protein level is controlled. To determine factors that may play a role in its regulation and expression, changes in p53 protein was investigated by using the androgen-insensitive JCA-1, DU-145, PC-3 and the androgen-responsive **LNCaP** cells. With the exception of PC-3 cells in which p53 is missing, multiple distinct forms of p53 were found in the other 3 prostate cell lines. A single p53 band was detected in the JCA-1 cell extracts, whereas two and three p53 immunoreactive bands were correspondingly observed in the DU-145 and **LNCaP** cells. The relative abundance and distribution of the different forms of p53 in the latter two cell types varied with proliferation of cells in culture. In the presence of charcoal-stripped fetal bovine serum (cFBS), **LNCaP** took on the morphology of **neuroendocrine** cells, a phenotypic change which was accompanied by a greater than 80% reduction in p53 expression, concurrent with elimination of the two slow migrating forms of p53. Induction of apoptosis in JCA-1 cells by treatment with the retinoid 4-HPR caused the virtual disappearance of p53, which coincided with specific processing of p53 into lower molecular weight 28 kD fragments. We propose that rapid and dynamic posttranslational changes in p53 may actively participate in determining mutually exclusive functional cellular events such as proliferation, differentiation, and apoptosis.

1997

1997

...ABSTRACT: by using the androgen-insensitive JCA-1, DU-145, PC-3 and the androgen-responsive **LNCaP** cells. With the exception of PC-3 cells in which p53 is missing, multiple distinct...
...whereas two and three p53 immunoreactive bands were correspondingly observed in the DU-145 and **LNCaP** cells. The relative abundance and distribution of the different forms of p53 in the latter...

...proliferation of cells in culture. In the presence of charcoal-stripped fetal bovine serum (cFBS), **LNCaP** took on the morphology of **neuroendocrine** cells, a phenotypic change which was accompanied by a greater than 80% reduction in p53...
DESCRIPTORS:
ORGANISMS: **LNCAP** (Hominidae...

10/3,K,AB/43 (Item 12 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

10912108 BIOSIS NO.: 199799533253
Growth stimulatory effect of the **neuroendocrine** substance serotonin on human prostate cancer cell lines.
AUTHOR: Abdul M; Hoosein N
AUTHOR ADDRESS: Univ. Texas, M. D. Anderson Cancer Center, Houston, TX 77030**USA

JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 38 (0):p574 **1997**
CONFERENCE/MEETING: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1997

Growth stimulatory effect of the **neuroendocrine** substance serotonin on human prostate cancer cell lines.
1997
DESCRIPTORS:
ORGANISMS: **LNCAP** (Hominidae...
MISCELLANEOUS TERMS: ...**NEUROENDOCRINE** SUBSTANCE

10/3,K,AB/44 (Item 13 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

10355600 BIOSIS NO.: 199698810518
Regulation of growth and differentiation of human prostate cancer cells by interleukin-1 and its antagonist.
AUTHOR: Chiao J W; Hsieh T C; Xu W; Sklarew R J
AUTHOR ADDRESS: New York Med. Coll., Valhalla, NY 10595**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 37 (0):p41 **1996**
CONFERENCE/MEETING: 87th Annual Meeting of the Amer

27 Genuine Article#: HW443 Number of References: 99
Title: SURVEY OF NEUROPEPTIDE GENE-EXPRESSION IN TUMOR-CELL LINES (Abstract Available)
Author(s): VERBEECK MAE; MUMMERY CL; FEIJEN A; BURBACH JPH
Corporate Source: UNIV UTRECHT,FAC MED,RUDOLF MAGNUS INST,VONDELLAAN 6/3521 GD UTRECHT//NETHERLANDS/; UNIV UTRECHT,FAC MED,RUDOLF MAGNUS INST,VONDELLAAN 6/3521 GD UTRECHT//NETHERLANDS/; NETHERLANDS INST DEV BIOL,HUBRECHT LAB/UTRECHT//NETHERLANDS/
Journal: PATHOBIOLOGY, **1992**, V60, N3 (MAY-JUN), P127-135
Language: ENGLISH Document Type: ARTICLE
Abstract: The presence of 3 different neuropeptide mRNAs with a strict cell-specific expression in vivo was investigated in 13 tumor cell lines from **neuroendocrine** and in 23 tumor cell lines from non-**neuroendocrine** origin. Northern blots showed no expression of mRNA for vasopressin (VP) in the 36 tested cell lines. Very low oxytocin (OT) mRNA hybridization signals were detected in the rat pituitary tumor cell line GH4C2 and the rat pancreas tumor cell line RIN5. Both the rat pituitary tumor cell line AtT-20 and the human myeloid leukemia cell line K562, contained proopiomelanocortin (POMC) mRNA. The low incidence of VP, OT and POMC gene expression in the tested tumor cell lines was not influenced by treatments inducing differentiation. In contrast, the cholecystokinin (CCK) gene which is widely present in nervous and endocrine systems was abundantly expressed in the human primitive neuroepithelioma cell line SK-N-MC and its clonal derivative SK-N-MC-IX-C. The results indicate that the expression of neuropeptide genes is very rare in tumor cell lines. The lack of expression in undifferentiated cells agrees with the appearance of expression after day 13 of the embryogenesis when maturation of neurons begins.

, **1992**
...Abstract: a strict cell-specific expression in vivo was investigated in 13 tumor cell lines from **neuroendocrine** and in 23 tumor cell lines from non-**neuroendocrine** origin. Northern blots showed no expression of mRNA for vasopressin (VP) in the 36 tested...
...Research Fronts: INSENSITIVE CALCIUM CHANNELS)
90-6677 001 (ANDROGEN RECEPTOR IN THE HUMAN PROSTATE TUMOR-CELL LINE **LNCAP**; INHIBITORY INSULIN-LIKE GROWTH-FACTOR BINDING-PROTEIN (IN-IGFBP); INVITRO SYSTEMS)
?

0/3,K,AB/51 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06472304 Genuine Article#: YV308 Number of References: 34
Title: Neurotensin is metabolized by endogenous proteases in prostate cancer cell lines (ABSTRACT AVAILABLE)
Author(s): Moody TW; Mayr CA; Gillespie TJ; Davis TP (REPRINT)
Corporate Source: UNIV ARIZONA,COLL MED, HLTH SCI CTR, DEPT PHARMACOL/TUCSON//AZ/85724 (REPRINT); UNIV ARIZONA,COLL MED, HLTH SCI CTR, DEPT PHARMACOL/TUCSON//AZ/85724; NCI,BIOMARKERS & PREVENT RES BRANCH/ROCKVILLE//MD/20850
Journal: PEPTIDES, **1998**, V19, N2, P253-258
ISSN: 0196-9781 Publication date: 19980000
Publisher: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010
Language: English Document Type: ARTICLE
Abstract: The formation and processing of neurotensin (NT) by three prostate cancer cell lines was investigated. Neurotensin (NT) immunoreactivity was detected in conditioned media and extracts of **LNCaP** cells. Using HPLC techniques, the immunoreactivity extracted from **LNCaP** cells coeluted with synthetic NT standard. Metalloendopeptidase 3.4.24.15 activity was detected in PC-3, DU-145 and **LNCaP** cells, whereas high levels of neutral endopeptidase 3.4.24.11 activity was detected only in **LNCaP** cells. NT was relatively stable when incubated with PC-3 or D-145 cells but was rapidly degraded by **LNCaP** cells to NT1-11 and NT1-10. Phosphoramidon inhibited the metabolism of NT by **LNCaP** cells. These data suggest that NT is present in and metabolized by **LNCaP** cellular enzymes. (C) 1998 Elsevier Science Inc.

, **1998**
...Abstract: cell lines was investigated. Neurotensin (NT) immunoreactivity was detected in conditioned media and extracts of **LNCaP** cells. Using HPLC techniques, the immunoreactivity extracted from **LNCaP** cells coeluted with synthetic NT standard. Metalloendopeptidase 3.4.24.15 activity was detected in PC-3, DU-145 and **LNCaP** cells, whereas high levels of neutral endopeptidase 3.4.24.11 activity was detected only in **LNCaP** cells. NT was relatively stable when incubated with PC-3 or D-145 cells but was rapidly degraded by **LNCaP** cells to NT1-11 and NT1-10. Phosphoramidon inhibited the metabolism of NT by **LNCaP** cells. These data suggest that NT is present in and metabolized by **LNCaP** cellular enzymes. (C) 1998 Elsevier Science Inc.

10/3,K,AB/52 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

06455441 Genuine Article#: YU408 Number of References: 29
Title: In vitro regulation of pericellular proteolysis in prostatic tumor cells treated with bombesin (ABSTRACT AVAILABLE)
Author(s): Festuccia C; Guerra F; DAscenzo S; Giunciuglio D; Albini A; Bologna M (REPRINT)
Corporate Source: UNIV AQUILA,DIPARTIMENTO MED SPERIMENTALE, CATTEDRA PATOL GEN, VIA VETOIO, COPPITO 2/I-67100 LAQUILA//ITALY/ (REPRINT); UNIV AQUILA,DIPARTIMENTO MED SPERIMENTALE, CATTEDRA PATOL GEN/I-67100 LAQUILA//ITALY/; IST NAZL RIC CANC,/I-16132 GENOA//ITALY/
Journal: INTERNATIONAL JOURNAL OF CANCER, **1998**, V75, N3 (JAN 30), P

07797192 Genuine Article#: 209PB Number of References: 48
Title: Silibinin decreases prostate-specific antigen with cell growth inhibition via G(1) arrest, leading to differentiation of prostate carcinoma cells: Implications for prostate cancer intervention (ABSTRACT AVAILABLE)
Author(s): Zi ZL; Agarwal R (REPRINT)
Corporate Source: AMC CANC RES CTR,CTR CANC CAUSAT & PREVENT, 1600 PIERCE ST/DENVER//CO/80214 (REPRINT); AMC CANC RES CTR,CTR CANC CAUSAT & PREVENT/DENVER//CO/80214; UNIV COLORADO,HLTH SCI CTR, CTR CANC/DENVER//CO/80262
Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **1999**, V96, N13 (JUN 22), P7490-7495
ISSN: 0027-8424 Publication date: 19990622
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418
Language: English Document Type: ARTICLE
Abstract: Reduction in serum prostate-specific antigen (PSA levels has been proposed as an endpoint biomarker for hormone-refraetory human prostate cancer intervention. We examined whether a flavonoid antioxidant silibinin tan active constituent of milk thistle) decreases PSA levels in hormone-refractory human prostate carcinoma **LNCaP** cells and whether this effect has biological relevance. Silibinin treatment of cells grown in serum resulted in a significant decrease in both intracellular and secreted forms of PSA concomitant with a highly significant to complete inhibition of cell growth via a G(1) arrest in cell cycle progression. Treatment of cells grown in charcoal-stripped serum and 5 alpha-dihydrotestosterone showed that the observed effects of silibinin are those involving androgen-stimulated PSII expression and cell growth. Silibinin-induced G1 arrest was associated with a marked decrease in the kinase activity of cyclin-dependent kinases (CDks) and associated cyclins because of a highly significant decrease in cyclin D1, CDK4, and CDK6 levels and an induction of Cip1/p21 and Kip1/p27 followed by their increased binding with CDK2. Silibinin treatment of cells did not result in apoptosis and changes in p53 and bcl2 suggesting that the observed increase in Cip1/ p21 is a p53-independent effect that does not lead to an apoptotic cell death pathway. Consersely, silibinin treatment resulted in a significant **neuroendocrine** differentiation of **LNCaP** cells as an alternative pathway after Cip1/p21 induction and G(1) arrest. Together, these results suggest that silibinin could be a useful agent for the intervention of hormone-refractory human prostate cancer.

, **1999**
...Abstract: tan active constituent of milk thistle) decreases PSA levels in hormone-refractory human prostate carcinoma **LNCaP** cells and whether this effect has biological relevance. Silibinin treatment of cells grown in serum...

...not lead to an apoptotic cell death pathway. Consersely, silibinin treatment resulted in a significant **neuroendocrine** differentiation of **LNCaP** cells as an alternative pathway after Cip1/p21 induction and G(1) arrest. Together, these...
...Identifiers--DEPENDENT KINASE INHIBITORS; HUMAN BREAST-CANCER; **LNCAP** CELLS; CYCLIN D1; TERMINAL DIFFERENTIATION; FLAVONOID ANTIOXIDANT; ANDROGEN RECEPTOR; CDK INHIBITORS; G1 ARREST; EXPRESSION

10/3,K,AB/49 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07778621 Genuine Article#: 207NE Number of References: 42
Title: The phosphatidylinositol 3'-kinase pathway is a dominant growth

factor-activated cell survival pathway in **LNCaP** human prostate carcinoma cells (ABSTRACT AVAILABLE)

Author(s): Lin JQ; Adam RM; Santiestevan E; Freeman MR (REPRINT)
Corporate Source: CHILDRENS HOSP,ENDERS RES LABS, 1151, 300 LONGWOOD AVE/BOSTON//MA/02115 (REPRINT); CHILDRENS HOSP,DEPT UROL, UROL LAB/BOSTON//MA/02115; HARVARD UNIV,SCH MED, DEPT SURG/BOSTON//MA/02115

Journal: CANCER RESEARCH, **1999**, V59, N12 (JUN 15), P2891-2897
ISSN: 0008-5472 Publication date: 19990615
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202
Language: English Document Type: ARTICLE

Abstract: Intracellular signaling pathways that mediate survival of prostate carcinoma (PCa) cells are poorly understood. We examined the potential role of the phosphatidylinositol 3' kinase (PI3K) pathway as a mediator of cell survival in **LNCaP** human PCa cells, which express a variety of properties characteristic of human prostate cancer. **LNCaP** cell cultures rapidly became apoptotic when treated with the specific PI3K inhibitors, wortmannin and LY294002. In contrast, apoptosis was not induced when the cells were treated with: (a) rapamycin, an inhibitor of the ribosomal S6 kinase pp70(86K), which acts downstream of PI3K; (b) PD98059, a specific inhibitor of the extracellular signal-regulated kinase/mitogen-activated protein kinase (Erk/MAPK) kinase (MEK); or (c) the antiandrogen, Casodex; or when the cells were cultured under androgen-depleted conditions, Apoptosis induced by PI3K inhibition was attenuated by: (a) dihydrotestosterone; or (b) the ErbB1 activating ligands [epidermal growth factor (EGF), transforming growth factor a, or heparin-binding EGF-like growth factor], In response to ErbB1 activation by ligand, the p85 regulat

9967 Genuine Article#: 309JL Number of References: 20
Title: Papaverine combined with prostaglandin ea synergistically induces neuron-like morphological changes and decrease of malignancy in human prostatic cancer **LNCaP** cells (ABSTRACT AVAILABLE)
Author(s): Shimizu T; Ohta Y; Ozawa H; Matsushima H; Takeda K (REPRINT)
Corporate Source: SCI UNIV TOKYO,FAC PHARMACEUT SCI, DEPT HYG CHEM, SHINJUKU KU, 12 ICHIGAYA FUNAGAWARA MACH/TOKYO 1620826//JAPAN/ (REPRINT); SCI UNIV TOKYO,FAC PHARMACEUT SCI, DEPT HYG CHEM, SHINJUKU KU/TOKYO 1620826//JAPAN/; UNIV TOKYO,FAC MED, DEPT UROL, BUNKYO KU/TOKYO 1138654//JAPAN/
Journal: ANTICANCER RESEARCH, **2000**, V20, N2A (MAR-APR), P761-767
ISSN: 0250-7005 Publication date: 20000300
Publisher: INT INST ANTICANCER RESEARCH, EDITORIAL OFFICE 1ST KM KAPANDNTIOU-KALAMOU RD KAPANDRITI, POB 22, ATHENS 19014, GREECE
Language: English Document Type: ARTICLE
Abstract: We are interested in the possibility of new prostate cancer therapy that would control tumor malignancy via the induction of terminal cell differentiation Here, we investigated the combined effect of various cAMP reagents an **LNCaP** human prostate carcinoma cells. Papaverine and prostaglandin E-2 (PGE(2)), combined synergistically induced morphological changes. Electron microscope study suggested that cells treated with both reagents become like **neuroendocrine** cells. We then investigated the effect of both reagents on proliferation and malignancy of **LNCaP** cells. The malignancy of cells was analyzed by soft agar colony-forming assay and an in vitro invasion assay Proliferation and malignancy of **LNCaP** cells treated with both reagents were significantly decreased in comparison to the proliferation and malignancy of untreated cells. Furthermore, the expression of oncogenes such as c-myc and Bcl-2 was suppressed in differentiated **LNCaP** cells. These results suggest that papaverine combined with PGE2 can synergistically induce neuronal differentiation as well as decrease the malignancy of human prostatic cancer **LNCaP** cells.

...Title: ea synergistically induces neuron-like morphological changes and decrease of malignancy in human prostatic cancer **LNCaP** cells
, **2000**
...Abstract: of terminal cell differentiation Here, we investigated the combined effect of various cAMP reagents an **LNCaP** human prostate carcinoma cells. Papaverine and prostaglandin E-2 (PGE(2)), combined synergistically induced morphological changes. Electron microscope study suggested that cells treated with both reagents become like **neuroendocrine** cells. We then investigated the effect of both reagents on proliferation and malignancy of **LNCaP** cells. The malignancy of cells was analyzed by soft agar colony-forming assay and an in vitro invasion assay Proliferation and malignancy of **LNCaP** cells treated with both reagents were significantly decreased in comparison to the proliferation and malignancy...

...the expression of oncogenes such as c-myc and Bcl-2 was suppressed in differentiated **LNCaP** cells. These results suggest that papaverine combined with PGE2 can synergistically induce neuronal differentiation as well as decrease the malignancy of human prostatic cancer **LNCaP** cells.

10/3,K,AB/48 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07797192 Genuine Article#: 209PB Number of References: 48
Title: Silibinin decreases prostate-specific antigen with cell growth inhibition via G(1) arrest, leading to differentiation of prostate carcinoma cells: Implications for prostate cancer intervention (

ABSTRACT AVAILABLE)
Author(s): Zi ZL; Agarwal R (REPRINT)
Corporate Source: AMC CANC RES CTR,CTR CANC CAUSAT & PREVENT, 1600 PIERCE ST/DENVER//CO/80214 (REPRINT); AMC CANC RES CTR,CTR CANC CAUSAT & PREVENT/DENVER//CO/80214; UNIV COLORADO,HLTH SCI CTR, CTR CANC/DENVER//CO/80262
Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **1999**, V96, N13 (JUN 22), P7490-7495
ISSN: 0027-8424 Publication date: 19990622
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418
Language: English Document Type: ARTICLE
Abstract: Reduction in serum prostate-specific antigen (PSA levels has been proposed as an endpoint biomarker for hormone-refraetory human prostate cancer intervention. We examined whether a flavonoid antioxidant silibinin tan active constituent of milk thistle) decreases PSA levels in hormone-refractory human prostate carcinoma **LNCaP** cells and whether this effect has biological relevance. Silibinin treatment of cells grown in serum resulted in a significant decrease in both intracellular and secreted forms of PSA concomita

10/3,K,AB/44 (Item 13 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

10355600 BIOSIS NO.: 199698810518
Regulation of growth and differentiation of human prostate cancer cells by interleukin-1 and its antagonist.
AUTHOR: Chiao J W; Hsieh T C; Xu W; Sklarew R J
AUTHOR ADDRESS: New York Med. Coll., Valhalla, NY 10595**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 37 (0):p41 **1996**
CONFERENCE/MEETING: 87th Annual Meeting of the American Association for Cancer Research Washington, D.C., USA April 20-24, 1996
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1996

1996
DESCRIPTORS:
ORGANISMS: **LNCAP** (Hominidae...
MISCELLANEOUS TERMS: ...PROGRESSIVE **NEUROENDOCRINE** CELL DIFFERENTIATION...

10/3,K,AB/38 (Item 7 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

11919190 BIOSIS NO.: 199900165299
Transdifferentiation of prostate cancer cells to a **neuroendocrine** (**NE**) cell phenotype in vitro and in vivo.
AUTHOR: Burchardt Tatjana; Burchardt Martin; Chen Min-Wei; Cao Yichen; De La Taille Alexandre; Shabsigh Ahmad; Hayek Omar; Buttyan Ralph
AUTHOR ADDRESS: New York City, NY**USA
JOURNAL: Journal of Urology 161 (4 SUPPL.):p56 April, **1999**
CONFERENCE/MEETING: 94th Annual Meeting of the American Urological Association, Inc. Dallas, Texas, USA May 1-6, 1999
SPONSOR: American Urological Association
ISSN: 0022-5347
RECORD TYPE: Citation
LANGUAGE: English
1999

0/3,K,AB/37 (Item 6 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

11928390 BIOSIS NO.: 199900174499
Interleukin-6 and cAMP-dependent protein kinase signaling converge to potentiate mitogen-activated protein kinase activation and fos gene transcription, and to enhance **neuroendocrine** differentiation of **LNCaP** prostate tumor cells.
AUTHOR: Deeble P D; Murphy D J; Parsons S J; Cox M E
AUTHOR ADDRESS: Univ. Va., Charlottesville, VA 22908**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 40p736 March, **1999**
CONFERENCE/MEETING: 90th Annual Meeting of the American Association for Cancer Research Philadelphia, Pennsylvania, USA April 10-14, 1999
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
1999

10/3,K,AB/34 (Item 3 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

12485160 BIOSIS NO.: 200000238662
Neuroendocrine-like survival of **LNCaP** prostate cancer cells
under in vitro androgen ablation conditions is dependent on PI3K-Akt.
AUTHOR: Huang Haojie(a); Murillo H(a); Smith D I(a); Tindall D J(a)
AUTHOR ADDRESS: (a)Mayo Clin, Rochester, MN**USA
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting (41):p405 March, **2000**
CONFERENCE/MEETING: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

Neuroendocrine-like survival of **LNCaP** prostate cancer cells
under in vitro androgen ablation conditions is dep

10/3,K,AB/33 (Item 2 from file: 55)
DIALOG(R)File 55:Biosis Previews(R)

12762078 BIOSIS NO.: 200000515701
Transdifferentiation of prostate cancer cells to a **neuroendocrine** cell phenotype in vitro and in vivo.
AUTHOR: Burchardt Martin(a); Burchardt Tatjana; Pulte Thomas; de da Taille Alexandre; Shabsigh Ahmad; Buttyan Ralph
AUTHOR ADDRESS: (a)Department of Urology, Columbia University, New York, NY **USA
JOURNAL: European Urology 38 (4):p531 October, **2000**
MEDIUM: print
CONFERENCE/MEETING: 15th Congress of the European Society for Urological Research Istanbul, Turkey October 05-07, 2000
ISSN: 0302-2838
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2000

10/3,K,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08217151 94354600 PMID: 8074475
Growth inhibition of human prostatic carcinoma cell lines by serotonin antagonists.
Abdul M; Anezinis P E; Logothetis C J; Hoosein N M
Department of Genitourinary Oncology, University of Texas, M.D. Anderson Cancer Center, Houston 77030.
Anticancer research (GREECE) May-Jun **1994**, 14 (3A) p1215-20, ISSN 0250-7005 Journal Code: 8102988
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neuroendocrine (**NE**) differentiation within the primary prostate tumor has been correlated with tumor progression and shortened patient survival. Serotonin (5-hydroxytryptamine, 5-HT), a known mitogen, is found in most **neuroendocrine** cells of the human prostate. We have previously found that human prostatic carcinoma cell lines, PC-3, DU-145 and **LNCaP**, display certain **NE** characteristics. In this study, we have examined the effects of several subtype-selective 5-HT receptor antagonists on the growth of the three lines. Of these, the 5-HT1A antagonist pindobind had the most marked antiproliferative effect in vitro. Pindobind also had marked growth-inhibitory effects on the aggressive PC-3 cell line in vivo, in athymic nude mice. Radioligand binding studies indicated the presence of 5-HT binding sites on all three cell lines. Our results suggest that 5-HT is involved in the growth of prostate tumor cells and may serve as a target for treatment.

10/3,K,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08500749 95255485 PMID: 7537687
Growth regulation and cellular changes during differentiation of human prostatic cancer **LNCaP** cells as induced by T lymphocyte-conditioned medium.
Hsieh T C; Xu W; Chiao J W
Department of Medicine, New York Medical College, Valhalla 10595, USA.
Experimental cell research (UNITED STATES) May **1995**, 218 (1) p137-43, ISSN 0014-4827 Journal Code: 0373226
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Human prostatic epithelial cells from an androgen-dependent **LNCaP** cell line were examined in response to conditioned medium (CM) derived from phytohemagglutinin (PHA)-stimulated lymphocytes. Addition of CM caused a greater than 70% reduction of cell proliferation by cell counting and cell cycle. These cells showed G1 phase arrest and the clonogenicity was reduced. The growth-modulating effect was dose-dependent and not due to cell lysis or apoptosis. The binding of androgen to androgen receptor on these cells showed approximately 50% reduction, underlining a proliferation reduction mechanism. The prostate-specific antigen (PSA) was downregulated to approximately 75% during the process. Cell morphology showed dendritic processes extending from cytoplasm and other **neuroendocrine** cell characteristics. The expression of several cytoskeleton and intracellular proteins increased as determined by immunostaining on slides and by ELISA procedures. These included vimentin, correlating to cell shape changes, cytokeratins 8 and 18, associated with differentiated cell types of prostate epithelia, and neuron-specific enolase and serotonin, associated with **neuroendocrine** cells. From these cellular changes, we can infer that the cell growth was modulated along with induction of terminal differentiation. Activated T cells were demonstrated to be important in providing the modulating activity. This growth modulator was semipurified and had an estimated molecular weight 13,000 to 24,000 Da. The activity was determined to be distinct from TGF, TNF, and some commonly known lymphokines. The interaction between lymphoid and prostatic cells in growth and development is described.

Growth regulation and cellular changes during differentiation of human prostatic cancer **LNCaP** cells as induced by T lymphocyte-conditioned medium.
May **1995**,
Human prostatic epithelial cells from an androgen-dependent **LNCaP** cell line were examined in response to conditioned medium (CM) derived from phytohemagglutinin (PHA)-stimulated...

... approximately 75% during the process. Cell morphology showed dendritic processes extending from cytoplasm and other **neuroendocrine** cell characteristics. The expression of several cytoskeleton and intracellular proteins increased as determined by immunostaining...

... with differentiated cell types of prostate epithelia, and neuron-specific enolase and serotonin, associated with **neuroendocrine** cells. From these cellular changes, we can infer that the cell growth was modulated along...

10/3,K,AB/27 (Item 27 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08360682 95123936 PMID: 7529853

Biomarkers associated with prostate cancer progression.

Zhau H E; Pisters L L; Hall M C; Zhao L S; Troncoso P; Pollack A; Chung L W

Urology Research Laboratory, University of Texas M.D. Anderson Cancer Center, Houston 77030.

Journal of cellular biochemistry. Supplement (UNITED STATES) **1994**, 19 p208-16, ISSN 0733-1959 Journal Code: 8207539

Contract/Grant No.: CA56307; CA; NCI; CA57361; CA; NCI; DK38649; DK; NIDDK

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In search of biomarkers that predict of human prostate cancer progression, we hypothesized that these markers must be expressed in prostatic epithelial cells during multi-step prostate carcinogenesis. Since both genetic and epigenetic factors have been implicated in human prostate cancer development, two osseous-metastatic experimental models were developed in our laboratory, one based on gene transfection and the other on stromal-epithelial interaction studies. In the genetic model, PC-3 cells transfected with point-mutated c-erbB-2/neu oncogene subsequently acquired the potential to metastasize from the prostate to soft tissues and the skeleton. In the epigenetic model, sublines derived from the parental androgen-dependent **LNCaP** cell line metastasized from the primary tumor to the lymph node and bone. Cells with known lineage relationships were cloned from both the primary and the metastatic tumors and were characterized extensively using cellular, biochemical, immunohistochemical, and molecular techniques. Relevant stage-specific biomarkers associated with prostate cancer progression in these two models were defined and used to evaluate human prostate tissues obtained from the clinic. In this communication, we focused our discussion on the potential importance of c-erbB-2/neu oncogene, vimentin, hepatocyte growth factor/scatter factor and its receptor, c-met oncogene, tumor angiogenesis and **neuroendocrine** factors as biomarkers for human prostate cancer progression.

1994,

... tissues and the skeleton. In the epigenetic model, sublines derived from the parental androgen-dependent **LNCaP** cell line metastasized from the primary tumor to

10/3,K,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09017744 96374099 PMID: 8780390
Neuroendocrine differentiation in human prostatic tumor models.
Noordzij M A; van Weerden W M; de Ridder C M; van der Kwast T H; Schroder F H; van Steenbrugge G J
Department of Urology, Erasmus University, Rotterdam, The Netherlands.
American journal of pathology (UNITED STATES) Sep **1996**, 149 (3) p859-71, ISSN 0002-9440 Journal Code: 0370502
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neuroendocrine (**NE**) cells can be identified in benign and malignant prostatic epithelia. Factors regulating their presence and their functions are poorly understood, mainly due to a lack of suitable experimental models. Fifteen in vitro and in vivo prostatic cancer tumor models, including a number of newly established in vivo models, were studied immunohistochemically for the presence of **NE** cells under different hormonal conditions. None of the in vitro models (PC-3, DU 145, **LNCaP**, and TSU) contained **NE** cells. Five of the seven xenograft models established at this laboratory contained **NE** cells. In three of these, **NE** cells were found only in the initial mouse passages. In the other two (PC-295 and PC-310), the **NE** phenotype was stable. **NE** features were confirmed by transmission electron microscopy and by Western analysis of chromogranin A expression. Immunohistochemical double-labeling experiments confirmed that **NE** cells in prostate cancer are post-mitotic (no Ki-67 expression) and do not express the androgen receptor. In the PC-295 and PC-310 models, short-term androgen withdrawal resulted in a rapidly increased number of **NE** cells. A time course experiment with PC-295-bearing mice strongly suggests that this increase occurred by induction of **NE** differentiation rather than by rapid proliferation and subsequent differentiation or selective persistence. In conclusion, these models are suitable to resolve fundamental questions with regard to the presence and functions of **NE** cells in human prostate cancer.

773663 98188256 PMID: 9520419

Etk/Bmx, a tyrosine kinase with a pleckstrin-homology domain, is an effector of phosphatidylinositol 3'-kinase and is involved in interleukin 6-induced **neuroendocrine** differentiation of prostate cancer cells.

Qiu Y; Robinson D; Pretlow T G; Kung H J

Department of Molecular Biology and Microbiology, Case Western Reserve University, School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106, USA.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Mar 31 **1998**, 95 (7) p3644-9, ISSN 0027-8424 Journal Code: 7505876

Contract/Grant No.: CA39207; CA; NCI; CA47179; CA; NCI; CA60171; CA; NCI; +

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Etk/Bmx is the newest member of Btk tyrosine kinase family that contains a pleckstrin homology domain, an src homology 3 domain, an src homology 2 domain, and a catalytic domain. Unlike other members of the Btk family kinases, which are mostly hemopoietic cell-specific, Etk/Bmx is preferentially expressed in epithelial and endothelial cells. We first identified this kinase in prostate cancer [Robinson, D., He, F., Pretlow, T. & Kung, H. J. (1996) Proc. Natl. Acad. Sci. USA 93, 5958-5962). Here we report that Etk is engaged in phosphatidylinositol 3-kinase (PI3-kinase) pathway and plays a pivotal role in interleukin 6 (IL-6) signaling in a prostate cancer cell line, **LNCaP**. Our evidence that PI3-kinase is involved in Etk activation includes: (i) Wortmannin, a specific inhibitor of PI3-kinase, abolished the activation of Etk by IL-6; (ii) a constitutively active p110 subunit of PI3-kinase was able to activate Etk in the absence of IL-6; and (iii) a dominant negative p85 subunit of PI3-kinase mutant blocked the activation of Etk by IL-6. Interestingly, IL-6 treatment of **LNCaP** induced a remarkable **neuroendocrine** -like differentiation phenotype, with neurite extension and enhanced expression of neuronal markers. This phenotype could be abrogated by the overexpression of a dominant-negative Etk, indicating Etk is required for

0314172 99307437 PMID: 10377442

Silibinin decreases prostate-specific antigen with cell growth inhibition via G1 arrest, leading to differentiation of prostate carcinoma cells: implications for prostate cancer intervention.

Zi X; Agarwal R

Center for Cancer Causation and Prevention, AMC Cancer Research Center, 1600 Pierce Street, Denver, CO 80214, USA.

Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Jun 22 **1999**, 96 (13) p7490-5, ISSN 0027-8424 Journal Code: 7505876

Contract/Grant No.: CA 64514; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Reduction in serum prostate-specific antigen (PSA) levels has been proposed as an endpoint biomarker for hormone-refractory human prostate cancer intervention. We examined whether a flavonoid antioxidant silibinin (an active constituent of milk thistle) decreases PSA levels in hormone-refractory human prostate carcinoma **LNCaP** cells and whether this effect has biological relevance. Silibinin treatment of cells grown in serum resulted in a significant decrease in both intracellular and secreted forms of PSA concomitant with a highly significant to complete inhibition of cell growth via a G1 arrest in cell cycle progression. Treatment of cells grown in charcoal-stripped serum and 5alpha-dihydrotestosterone showed that the observed effects of silibinin are those involving androgen-stimulated PSA expression and cell growth. Silibinin-induced G1 arrest was associated with a marked decrease in the kinase activity of cyclin-dependent kinases (CDKs) and associated cyclins because of a highly significant decrease in cyclin D1, CDK4, and CDK6 levels and an induction of Cip1/p21 and Kip1/p27 followed by their increased binding with CDK2. Silibinin treatment of cells did not result in apoptosis and changes in p53 and bcl2, suggesting that the observed increase in Cip1/p21 is a p53-independent effect that does not lead to an apoptotic cell death pathway. Conversely, silibinin treatment resulted in a significant **neuroendocrine** differentiation of **LNCaP** cells as an alternative

10/3,K,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10372578 99374667 PMID: 10447001

Acquisition of **neuroendocrine** characteristics by prostate tumor cells is reversible: implications for prostate cancer progression.

Cox M E; Deeble P D; Lakhani S; Parsons S J

Cancer Center and Department of Microbiology, University of Virginia Health Sciences Center, Charlottesville 22908, USA.

Cancer research (UNITED STATES) Aug 1 **1999**, 59 (15) p3821-30, ISSN 0008-5472 Journal Code: 2984705R

Contract/Grant No.: PO1 40042; PHS; R21 69848; PHS; RO1 76649; PHS

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Neuroendocrine (**NE**) cells occur as scattered foci within prostatic adenocarcinoma, similar to their distribution within ductal epithelial cells of the normal prostate. However, the density of **NE** cells is often greater in prostate carcinomas than in normal tissue, and the frequency of **NE** cells correlates with tumor grade, loss of androgen sensitivity, autocrine/paracrine activity, and poor prognosis. Although **NE** cells are nonmitotic, proliferating cells are found in direct proximity to them, suggesting that **NE** cells provide paracrine stimuli for surrounding carcinoma cells. In vitro, differentiation of the **LNCaP** and PC3M prostatic tumor cell lines to a **NE** phenotype can be induced by dibutyryl cyclic AMP (cAMP), suggesting that physiological agents that increase intracellular concentrations of cAMP might regulate **NE** differentiation in vivo. Indeed, we demonstrate in this report that **LNCaP** cells acquire **NE** characteristics in response to treatment with physiological and pharmacological agents that elevate intracellular cAMP, agents such as epinephrine, isoproterenol, forskolin, and dibutyryl cAMP. The androgen-independent **LNCaP**-derived cell line C4-2 also responded to these agents, indicating that cells representing